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March 25, 2008

Mr. Richard Keller
Senior Officer for Scientific & Medical Research Facilities
California Institute for Regenerative Medicine
210 King Street
San Francisco, California 94107

RE: Response to the Staff Analysis of CIRM Application #FA100613-1 (CIRM Institute)

Dear Mr. Keller,

On behalf of the University of California, Los Angeles (UCLA) and the Eli & Edythe Broad Center of Regenerative Medicine and Stem Cell Research (Broad Stem Cell Research Center [BSCRC]), I thank you for the Staff Analysis of our CIRM Part 2 Major Facilities application. We appreciate the difficult task of summarizing and providing analyses of the complex proposals on such a short timeline.

In general we found the Analysis provided an accurate description of our proposal. The Analysis, however, raised several concerns and questions that we would like to clarify and provide you and the Facilities Working Group with the attached responses.

Thank you for providing us with the opportunity to respond to the Analysis. Please do not hesitate to contact me if you have any questions.

Sincerely,

Steven Peckman
Associate Director

cc: Chancellor Gene Block
Vice Chancellor Steven Olsen
Director Owen Witte

Urgency – The applicant has completed planning and is awaiting CIRM funding before releasing bids. Is there a risk that the CIRM-funded space may be subject to delays related to delivering the overall project?

As noted in the Part 2 application, the CIRM-UCLA Institute will occupy one research laboratory floor and a portion of the basement vivarium in the Life Sciences Replacement Building (LSRB) in the center of the UCLA south campus. A construction contract for LSRB was bid in February 2007 and construction commenced in June 2007. Beneficial occupancy is scheduled for May 2010. The scope of work included in the lump-sum construction contract will result in a functional facility; **there is no separate bid related to the proposed CIRM-funded space**.

Risk related to project approvals for the overall LSRB project including Regental approval, procurement of financing, environmental approvals, site conditions and bid risk have all been mitigated and their respective milestones have been met. **Project planning, design, working drawings, and Regental and agency approvals represent approximately two and a half years of effort prior to the award of bid.**

As described in the Part 2 application, the following fundamental milestones were met before submission of the Part 1 Major Facilities application:

1. September 2005: UC Regents approval
2. September 2005: Focused Tiered Environmental Impact Report (Final EIR)
3. February 2007: Construction contract bids
4. April 2007: Campus accepts base bid and two alternatives
5. May 2007: Authorization from the UC Office of the President
6. May 2007: Award of bid
7. June 2007: Construction began

With all of the preliminary requirements and milestones met and construction on-going, the risk that CIRM-funded space may be subject to delays related to delivering the overall project is ***very*** low. As of March 2008, the construction contract is 17% complete (See Figures 1 and 2). **Based on the current construction schedule, LSRB will be available for equipment installation in January 2010 (approximately six months ahead of the July 2010 deadline) and will be ready for beneficial occupancy in May 2010, (approximately two months ahead of the July 2010 deadline)**.

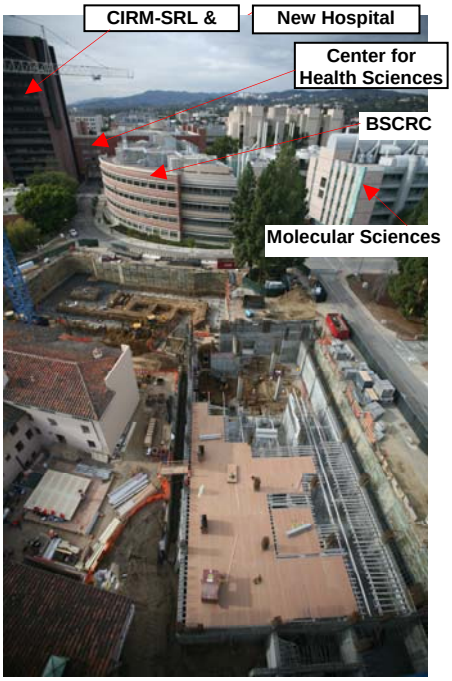

Figure 1: In the foreground and middle, LSRB under construction, January 2008, with adjacent buildings.

We would like to reiterate the experience and qualifications of our project team, with an emphasis on the track record of projects completed with our general contractor on the LSRB project, PCL Construction. PCL has recently completed three other campus projects representing a total project cost of $34,9 million, $102.6 million and $7.2 million. Each of these projects received their temporary certificates of occupancy that allowed building occupants to move-in according to their

respective project schedules. Our senior management and project delivery team has successfully executed a high volume of complex projects since UCLA Capital Programs was established in 1986, deploying approximately $4.2 billion to complete a variety of new construction, renovation and infrastructure projects on the UCLA campus.

Figure 2: LSRB under construction, March 11, 2008.

Cost- How will the FWG weigh the Group 2 Equipment costs, which are more than twice the average of other projects on a square foot basis. The amount includes over $6.2 million for core facilities.

Though UCLA's significant investment in innovative Group 2 Equipment for our Cores that will serve to drive the science forward and as the initial equipment set-up for investigators may be higher on a square foot basis than the other submitted values, the investment will result in a significant return through future cost savings to CIRM grantees and thus, California tax payers, as explained below.

The proposed Facility will only include new Core resources rather than duplicate existing programs. As indicated in the Part 1 and 2 applications, the central campus location (see Figure 3) of the proposed Facility based core resources will ensure ready access to not only Institute stem cell investigators but also to stem cell investigators in adjacent related buildings. The Core resources provide individual faculty with access to highly specialized, cutting-edge equipment that could not be duplicated by any individual due to prohibitive cost and will provide a cost savings to CIRM grantees. For example, the subsidy provided by the BSCRC through support of key personnel and service contracts for the Core Resources reduces the cost for any individual investigator by 50-60%. Please note: The Vector Core outlined in the Part 2 application will be moved from its current location and expanded in provided services and functions.

For example, the innovative Advanced Mouse Genetics Core will apply the VelociGene technology developed by Regeneron Pharmaceuticals, Inc., to genetically modify mouse embryonic stem cells with high efficiency. This core resource will be unique to the CIRM Institute and will be of vital importance to campus and Caltech investigators developing

mouse stem cell models. The technology in this core presents a dramatic decrease in the time necessary to create and evaluate mutant strains of mice thus saving money and accelerating research results thus reducing significant overall mouse breeding and housing costs, approximately ~25% of the cost to individual investigators. The advanced mouse genetic technologies accelerate research and provide the technology to answer crucial scientific questions faster.

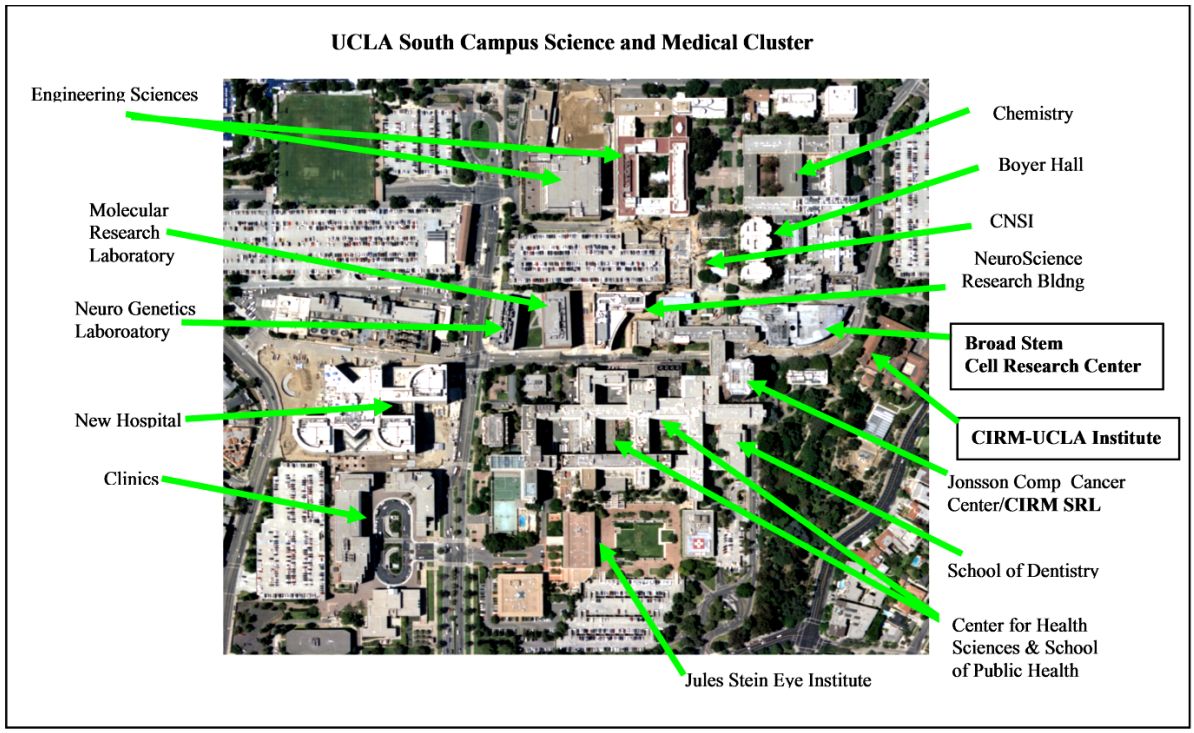

Figure 3: Aerial view of UCLA south campus with the proposed CIRM Facility & the CIRM-SRL BSCRC, JCCC, Hospital, Clinics, CNSI, Engineering, Chemistry, etc.

In addition, our Bioengineering Core will take cell separation and manipulation to the leading edge by establishing a core to focus our considerable expertise in bioengineering on stem cell biology. For example, the core will support the synthesis of new surfaces for growing hESC and the development of new cell separation technologies, including the use of microfluidics and the development of optical tweezers to micromanipulate cells. The microfluidics component of the Bioengineering Core will enable the movement of small amounts of fluid and cells to facilitate hESC cell separation, merging and mixing, and culturing in small volumes. These small volume techniques are being applied in collaboration with CalTech in the DNA Encoded Antibody Libraries (DEAL) approach for ultrasensitive detection of protein, DNA, RNA, and single cell analysis.

In complementary studies, we are developing floating electrode optoelectronic tweezers (FEOET) to move cells and microliter droplets on a freely configurable platform that uses very low power to grow and manipulate hESCs. These biophysical approaches are dependent on the Bioengineering core. Little is known about the role for mitochondria in the control of quiescence, survival, self renewal, or differentiation in hESC despite the fact that alterations in the maternally-encoded mitochondrial genome will likely affect hESC function and potential for long-term therapy. In collaboration with D. Wallace (CIRM Investigator Grant) of the UCI Stem Cell Institute, we are defining the sequence for the mitochondrial genome of hESCs with desirable

nuclear genomic and epigenomic qualities to assist in the selection of lines for translational and therapeutic usage. This new methodology allows the simultaneous testing of external stimuli that effect growth and development of pluripotent cells for large scale testing. The innovative technology requires less physical space and materials as compared with the labor intensive, expensive (reagents), equipment and conventional technology. The microfluidics Core will reduce the cost of reagents by 1000 fold thus allowing a large number of quantitative measurements that ultimately will result in a cost savings to CIRM and acceleration of scientific discovery.

Further, our Vivarium is crucial to our mission of evaluating new therapies and concepts in pathology through advanced mouse models of disease and cell transplantation. Campus vivaria are impacted resulting in considerable backlog for use and thus a deceleration in scientific research. The Facility Vivarium and dedicated procedure rooms will serve to address the campus backlog by providing rooms specifically devoted to stem cell investigators who will have immediate access to designated space and adjacent mouse housing. The Facility vivarium and dedicated procedures rooms are particularly important for the success of the Advanced Mouse Genetics Core. The dedicated Vivarium will, for example, also provide a cost saving for stem cell research through dedicated and centralized cage washing, maintenance, and autoclave and though under the direct authority of the campus veterinarian, the Facility Vivarium will be operated by BSCRC personnel with a resulting anticipated cost savings from normal Department of Laboratory and Animal Medicine (DLAM) cost structures. In similar paradigms here at UCLA, a 30% savings has been realized due to the opportunity for cage changing personnel to conduct additional tasks such as breeding, tissue acquisition, and analysis in the laboratory.

The structure of this proposal, specifically the new and innovative Core resources, speaks to the highly collaborative UCLA research environment. Existing campus cores are essential for the success of our stem cell program and are all highly interactive with the program. There are many examples of shared Core resources in Section 4 that are currently used and will in the future be used by Facility investigators, including but not limited to, the Nude/SCID Mouse Core Facility and the Virology/BSL 3 Cores in the Biomedical Sciences Research Building (BSRB) and CNSI. It would be impracticable and inefficient to move already existing and fully functioning ultra-clean fabrication facilities in the Engineering building and the PET/PET CT Imaging Facility in the Crump Institute to the Facility (less than a five minute walk) or try to fit such technologies in one space. For example, the cost of creating a new imaging center in the Facility rather than maintain its current location less than a five minute walk from the CIRM-UCLA Institute would cost ~$5-10M with similar costs for the BSL3 and Nude SCID mouse cores. CIRM will see a cost savings from the lack of redundancy and better cost structure resulting from the management of the most critical facilities to achieve our mission.

Leverage-How will the FWG weigh the relatively low leverage for a facility of modest size that offers less square footage per PI than other proposals?

In addition to the substantial investments and commitments made through the campus' support of stem cell related research (e.g., ~$266M available to support stem cell related

research over the last 3 years, including: $20M/over 5 years and 12 State funded new full-time faculty positions with ~$12-20M start-up packages and substantial gifts [Broad Foundation: $20M/over 5 years], ~$206M related building infrastructure represented by the LSRB and the Cesar Pelli designed BSRB [~64Kasf/50% occupancy by BSCRC members and stem cell related investigators including seven CIRM awardees] directly across the street from the CIRM-UCLA Institute, $6.5M support for related Core Facilities through the Chancellor's Biosciences Initiative) and in strict compliance with *allowable* leverage per this RFA, UCLA is committed to supporting CIRM's objective of encouraging investments in the Facility through our documented leverage funds.

UCLA Support of Stem Cell Related Research	
Source	**Total Funds**
UCLA – BSCRC: - Infrastructure (construction & equipment) - Administrative & Technical Support - Seed Grants - Faculty recruitment	$20M/over 5 years
SoM, College, SoE support of new 12 faculty recruitment	$12M+
Broad Foundation – BSCRC, includes - Innovation Awards - Essential equipment - Technical support - Seed Grants	$20M/over 5 years
LSRB/CIRM - UCLA Institute	$125.8M
Biomedical Sciences Research Building (BSRB)	$80M
Biosciences Initiative	$6.5M
JCCC Research Seed Grants to Stem Cell Scientists	~$1M
UCLA (construction commitment to CIRM – UCLA SRL	~.5M
Total	**~$266M**

Our allowable leverage funds total $6,258,949 and include the amount spent to date on the main project, the cost to design the additional floor to be assigned to the UCLA CIRM Institute, and the amount to cover the proportional share of site preparation work that preceded construction of LSRB. It also includes a total of $3,492,500 for additional Group 2 equipment in the amount that is necessary to make the laboratories fully operational, including $1,913,389 of equipment purchased from August 24, 2007 to date, and $1,579,111 of match in addition to the 20% requirement. Further, UCLA has identified $768,300 in existing Group 2 equipment that will be relocated to the Facility in support of stem cell research. This value is not reflected in the project budget, but represents another level of commitment that UCLA has to this project's long term.

Functionality - How will the FWG weigh the relatively small amount of space per PI and the relative lack of interactive spaces? "Opportunities for interaction are somewhat limited and those that are included in the design are dispersed and may not afford a desirable level of interaction."

As indicated in the Part 2 application, the proposed space assignments are designed to maximize efficiency of the dedicated stem cell researchers in a highly interactive space with an open laboratory concept. We view large tracts of space assigned to

investigators without regard to specific program objectives as wasteful, ultimately generating a "walled city state mentality" that blocks interaction and collaboration between groups. Smaller highly interactive groups sharing space is our choice to foster cross pollination of ideas and technologies and to adapt to new technologies and ideas.

Efficiency and Reducing the Duplication of Resources

The urgency to develop new therapies through stem cell science requires a break from traditional academic models of theory and practice, including laboratory structures. The principles that inform our space allocation require a fundamental shift from the traditional model of one investigator-one lab which we view as inflexible, not conducive to collaboration, and ultimately suppresses efficient cross fertilization of ideas and technologies, to a major new paradigm in space utilization of shared laboratory facilities and team attack of critical problems where students, post-docs and technical staff from multiple and various groups work within the same space because they chose to work together on a common problem from different perspectives and expertise. The new paradigm is a much more business like model used to attack multi-disciplinary problems and drive discoveries as seen in the high technology and biotechnology industries.

The specific faculty assignments are based on the nature of the stem cell program that the investigator has proposed and the number of personnel required for the work. Though the noted investigators will have their primary stem cell laboratories in the Institute, some will have key personnel working on other projects which can be better supported in other buildings or that provide specialized facilities not found in the LSRB. Furthermore, efficient use of space and better cross disciplinary approaches have been planned by putting specific investigators together when they have identified key problems on which they want to collaborate. Examples include, G. Fan and H. Kornblum working on biochemical and biological understanding of neuron-stem cells or J. Zack, O. Witte, and Z. Galic on blood stem cells. Other examples that will avoid duplication of facilities include:

- U. Banerjee will conduct his blood stem cell work in the Facility while his important model-system zebra fish research will occur across the street in the new BSRB.
- O. Witte will locate his epithelial tissue stem cell activities in the Institute and his molecular imaging work at other sites where specialized facilities are located.
- J. Zack and Z. Galic also have space in BSRB for their work using infectious HIV which is carried out in a BSL3 laboratory environment.
- This is even more important for clinically oriented investigators (J. Zack, A. Ribas, R. MacLellan, Z. Galic) who will also use the GMP and CIRM-UCLA SRL FDA compliant Good Tissue Practices (GTP) laboratories (across the street in the Factor Building) for those aspects of their research connecting to clinical trial materials.

Hence the assigned square footage for even senior investigators reflects the nature of their stem cell activities and acknowledging that other related research will occur within a five minute walk of the Facility in order to avoid duplication of resources.

We view the space allocation as highly efficient because of the specific plans for the shared Core facilities of various high technology analyses, including but not limited to FACS, confocal microscopy, microarrays, sequencing, SKY karyotyping, CGH, vector production, and computational technologies as joint and shared to avoid duplication of space and the wasteful use of lab benches in individual investigator labs for such equipment. The allocation also enables the BSCRC to more effectively use limited

resources to support the key technical personnel for such facilities in a shared and Center-wide manner rather than duplicating efforts in multiple laboratories.

As noted in our application, we have allocated space for 3-4 junior faculty in the Facility. UCLA's young and emerging stem cell scientists will be intentionally assigned small yet highly interactive space to foster both collaborative research and will maximize the efficiency and opportunity for mentorship and cross training in the developmental space. The space allocation is not permanent and will be dependent on the quality of the on-going stem cell research. The smaller space allotment for developing investigators is based on the very realistic concept that individuals will not build large lab groups but rather will have at most 2 or 3 individuals under their guidance as they learn to coordinate the research of others and transition from fellow to independent faculty positions.

For our new junior faculty positions, we anticipate that they will develop a group size of 5 to 6 individuals which can easily and comfortably be accommodated in the amount of space assigned because we have taken care to design the building with excellent shared facilities to avoid duplication of effort by individual labs for commonly used technical approaches.

As stated in Part 1 and 2 of UCLA's application, the CIRM-UCLA Institute will include laboratory space for new, mid-career, and senior faculty. The BSCRC has successfully recruited six new junior faculty with an active open search for the remaining six positions. Facility space has been allocated for three new faculty and four developing faculty. The diversity of research conducted by investigators in the Facility requires various allocations of space. For example, some faculty will be working at the preclinical/clinical interface in order to bring new therapeutics online while a bioinformaticist does not require the laboratory space necessary to conduct wet lab research and thus the assigned square footage has been determined accordingly.

Design Reflects Function

The LSRB, the building in which the CIRM - UCLA Institute will reside, has been designed with large, open-bay laboratory spaces to allow multiple scientists to work in a shared laboratory environment, with the main laboratory spaces uninterrupted by doors and walls. The building was developed to support investigation in the biological and physiological sciences, clearly integrated components of regenerative medicine, and the building's modular and flexible laboratory spaces promote interaction. The open laboratory space promotes flexibility and facilitates research integration and interaction through the modular nature of the laboratories that permit the space assigned to individual investigators to increase or decrease (flexible space) according to need so that the research laboratory environment can respond to changes in technology, research missions and personnel over the life of the building. Additionally, movable and vertically adjustable casework as well as distribution of laboratory utilities from overhead carriers promote reconfiguration based on current scientific rather than restrict future research due to limits of interior design.

LSRB's scientific support space has been provided and configured to facilitate and enhance these changing requirements. Support spaces are part of the modular lab planning grid, and consist of fume hood alcoves, and procedure, equipment, glass wash and controlled environmental rooms. Dry laboratory space has also been provided to support programs with computational requirements. The basement-level vivarium includes a barrier mouse facility, as well as holding rooms for rodents, birds and several aquatic species. Procedure and surgery rooms are also available inside the vivarium. LSRB's offices have been designed on the same module as the laboratories with a

standard size for each. Standardized office design provides flexibility in assignment, ease of relocation as research projects change, and enhanced potential for interaction and collaboration. Private offices will be assigned to faculty. Administrative support space on each of the floors, including the third floor, includes two conference rooms and a break room. Finally, investigator office spaces are immediately across the hall from the laboratories facilitating access to assigned faculty by their colleagues, pre- and post-doctoral laboratory staff, as well as technical staff and Core resources staff. Such proximity creates an optimal environment for scientific and technical exchange, trouble-shooting, and problem solving.

Ultimately, the 15 stem cell faculty laboratories in the proposed Facility as well as access to 6 critical, innovative, and unique core facilities including advanced mouse genetics and microfluidics, will promote synergy among various labs both within and outside the Facility, and serve as a focal point for our ongoing efforts in translational cellular research. The central location of the Facility, in close, on-site proximity to the UCLA professional schools (medicine, engineering public health, dentistry, nursing), the college of letters and science, and other institutes/centers, will allow faculty easy access to their colleagues in adjacent buildings as well as to the GMP suite, hESC stem cell bank and derivation cores, and the CIRM sponsored GTP-SRL directly across the street.

Sustainability & Innovation – "The project may achieve a LEEDS certification at the Silver level, but the application notes it is one point short of achieving that level. At a minimum, the building will meet the equivalent rating of 'certified' under the LEED Standards."

CIRM's staff analysis of our application indicates that the CIRM-UCLA Institute may achieve a LEED certification at the "SILVER" level, but this is one point short of that level. It is important to note that the Institute will reside within the LSRB, a laboratory building totally dedicated to research, and not a mixed-use building that would be required to meet less stringent standards. As a result, the "certified" rating identified in our application is in accordance with the 21st Century (Labs 21) program scoring scale.

As described in the Part 2 application, the LSRB complies with the UC Policy on Sustainable Practices, which includes both a minimum UC-equivalent LEED rating for new construction and high performance energy standards under the Labs 21 program. The Labs 21 component, applicable to all buildings with energy intensive uses such as LSRB, increases the possible points from 69 to 85, resulting in an increase in the threshold values for certification and ratings of silver, gold and platinum. Points are given for appropriate sizing of lab equipment, for selection of efficient equipment, for efficient use of energy supply, and for the commissioning and efficient operation of fume hoods. Based on these criteria, LSRB currently has been assigned 40 points, within one point of achieving a silver rating. The estimated points achievable represent a conservative projection, and will likely be exceeded upon completion of the building. In accordance with the rating system, the final score cannot be determined until the building is fully commissioned and operational.

The staff analysis of our application also indicates that LSRB's design elements of interactive space, energy efficient ventilation systems and the use of day-lighting techniques are typical for this type of building. We would like to call attention to another innovative aspect of the design involving the development of a highly flexible building plan, a plan that has enabled us to meet the requirements of stem cell research without necessitating modification to the design of the building or the space proposed to accommodate the CIRM-UCLA Institute. The building has been designed to provide

flexibility in assignment and ease of relocation as specific research projects evolve and change over time.